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Strategies for Epidemiologic Studies of Lead in Bone in Occupationally Exposed Populations

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Lead exposure is widespread among industrial populations in the United States. X-ray fluorescence (XRF) analysis of the lead content of bone offers a promising approach to acquisition of individualized data on chronic lead absorption in occupationally exposed populations. Dosimetric data obtained by XRF will permit accurate definition of dose-response relationships for such chronic consequences of lead exposure as central and peripheral neurologic impairment, renal disease, hypertension, and possibly reproductive dysfunction. Additionally, data on bone lead content obtained by XRF will permit validation of models describing the body lead burden and will allow direct assessment of the efficacy of therapeutic chelation. XRF data may also permit assessment of the possible role of genetic polymorphism of the enzyme delta-aminolevulinic dehydrase as a determinant of the pharmacokinetics and toxicity of lead. In both cross-sectional and prospective epidemiologic studies of body lead burden in occupationally exposed populations, the K-XRF instrument appears to be the technology of choice.

Introduction

Lead is a major occupational toxin. More than 1.4 million industrial workers in the United States have potential occupational exposure to lead (*1*). These populations constitute unique groups in which to undertake epidemiologic and toxicologic studies. The groups are precisely defined. Data on the duration of each worker's employment and information on job assignments can be obtained reliably. Data on past exposures to lead in air have been obtained routinely in the lead-using industries in the United States for at least a decade, and periodic determinations of blood lead levels have been required since 1978 (*2*); these data are available for epidemiologic analysis. Finally, industrial workers have exposures to lead which typically are higher and more prolonged than those of the general population; thus, worker populations constitute uniquely important groups for assessing toxic effects of lead at the upper end of the dose-response relationship.

In this review, I summarize current knowledge of the toxicity of lead in industrial populations and note the gaps in this knowledge base. I then discuss strategies for future research to close these gaps, with particular emphasis on approaches that may measure chronic exposure to lead through determination of the lead content of bone by X-ray fluorescence (XRF) analysis.

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Industrial Lead Poisoning

Lead has long been recognized to cause poisoning in industrial workers. More than 200 years B.C., Nikander, a Greek poet and physician, described coma, paralysis, and colic in lead workers (*3*). Descriptions of high-dose industrial lead poisoning were provided also by Ramazzini in the early 1700s (*4*), by Charles Turner Thackrah in Victorian England (*5*), and by Alice Hamilton in the United States early in this century (*6*). The classic clinical manifestations of industrial lead poisoning include colic, anemia, peripheral neuropathy, encephalopathy, renal impairment, hypertension, and reproductive disability.

Subclinical Toxicity

More recently, the recognition has become widespread that in addition to its clinically evident toxicity, lead also causes a spectrum of adverse effects at levels of exposure insufficient to produce obvious signs and symptoms. The premise underlying this recognition is that there exists a continuum of toxicity, in which clinically apparent effects have their asymptomatic, subclinical counterparts. Thus, clinically obvious manifestations of lead poisoning such as anemia, peripheral neuropathy, and renal failure lie at the upper end of the range of toxicity, while such covert effects as slowed nerve conduction, impaired synthesis of heme, and altered excretion of uric acid are their subclinical correlates (*7,8*).

Hematologic Toxicity

In the red blood cells, anemia is the classic clinical manifestation of lead toxicity. The severity and prevalence of this anemia are correlated directly with the blood lead level (*9*). The anemia of lead is produced by two mechanisms: impairment of heme biosynthesis and acceleration of red blood cell destruction. Lead-induced inhibition of heme biosynthesis is due first to inhibition of the cytoplasmic enzyme, delta-aminolevulinic acid dehydratase (ALA-D) (*10,11*). This effect is dose related. It is noted initially at blood lead levels of 10 to 20 μg/dL and is virtually complete at levels of 70 to 90 μg/dL (*12*).

The mitochondrial enzyme ferrochelatase is the second enzyme in the heme biosynthetic pathway inhibited by lead. Ferrochelatase catalyzes the transfer of iron from ferritin into protoporphyrin to form heme (*13*). Inhibition of ferrochelatase causes increased excretion of coproporphyrin in the urine and accumulation of protoporphyrin in the erythrocytes (EP). In adult males, EP levels begin to rise above background at blood lead levels of 25 to 30 μg/dL (*14*). Close correlations have been found between blood lead and EP concentrations (*15*).

Neurologic Toxicity

In the peripheral nervous system, the motor axons are the principal target of lead. Lead-induced pathologic changes in these fibers include segmental demyelination and axonal degeneration (*16*). Extensor muscle palsy with wrist drop or ankle drop is the clinical manifestation of this toxicity.

Recent studies of the peripheral nerves in persons exposed to lead have used electrophysiologic probes to determine whether lead causes covert abnormalities in function. In the first of these studies, Seppäläinen et al. found evidence for asymptomatic slowing of motor nerve conduction velocity in workers whose blood lead levels had never exceeded 70 μg/dL (*17*). Araki et al. found similar, asymptomatic dose-related slowing of motor nerve conduction (*18*). Following those studies, Seppäläinen et al. examined in further detail the dose-response relationship between blood lead levels and conduction velocity (*19*). They found slowed conduction in the small motor fibers of the ulnar nerve to be the most sensitive peripheral index of the neurotoxicity of lead; in a cross-sectional study, ulnar nerve conduction velocity was depressed at blood lead levels below 50 μg/dL. Most recently, in a prospective study of new entrants to the lead industry, Seppäläinen et al. found slowing of ulnar nerve conduction velocity at blood lead levels as low as 30 to 40 μg/dL (*20,21*).

In the central nervous system, extensive research has sought to determine whether lead causes asymptomatic impairment in function at doses insufficient to produce clinically evident encephalopathy. In one of the earliest of these studies, Hanninen et al. found a correlation between lead exposure and diminished neuropsychologic performance in 49 asymptomatic workers, all of whom had blood lead levels below 70 μg/dL (*22*). The functions most severely impaired were those dependent on visual intelligence and visual-motor coordination. Similar findings were reported by Valciukas et al. (*23*), Arnvig et al. (*24*), and Araki et al. (*25*). Baker et al. reported an increased prevalence of fatigue and short-term memory loss in smelter workers exposed to lead; the prevalence of these abnormalities increased with blood lead levels (*9*).

Renal Toxicity

Chronic nephropathy, which may progress to kidney failure, is the classic renal manifestation of lead toxicity. It appears to result from long-term, relatively high-dose exposure to lead.

The cells lining the proximal tubules appear to be the tissue in the kidney most highly sensitive to lead (*26*). At blood lead levels below 25 μg/dL, lead inhibits the metabolic activation of vitamin D, a transformation which occurs in these cells (*27*). Also in these cells, at blood lead levels of 40 to 80 μg/dL, lead induces the formation of dense intranuclear inclusion bodies consisting of lead-protein complex (*26*). Hyperuremic gout, apparently resulting from increased reabsorption of uric acid by the tubular cells, is a third metabolic correlate of lead-induced renal impairment (*26*).

The evolution of lead nephropathy is usually silent. The central event appears to be the progressive destruction of tubular cells and their replacement by fibrosis (*28*). Clinical manifestations of impairment, consisting of elevations in blood urea nitrogen (BUN) or serum creatinine, do not ordinarily become evident until 50 to 75% of the nephrons have been destroyed. Pathologically, the late stage of lead nephropathy is characterized by interstitial fibrosis with atrophy and dilation of the tubules and relative sparing of the glomeruli; in this stage, intranuclear inclusions are infrequent (*26*).

Excess mortality from renal disease has been observed in four epidemiologic studies of lead workers (*29–32*). In each of these investigations, a 2- to 3-fold increase has been noted in deaths from chronic nephritis. In the study by Selevan et al., a positive association was observed between duration of employment in a lead smelter and mortality from nephritis (*32*).

Lead and Hypertension

Long-term, high-dose exposure to lead was reported early in this century to be associated with an increased incidence of hypertension and cerebrovascular accident (*33*). With the reduction in lead exposure that has occurred in most industries, these associations are now noted less commonly. Several recent epidemiologic studies have, however, found evidence that lead absorption, even at relatively low levels, is associated with significant elevation in blood pressure (*34*). Toxicologic studies have also documented an association between

increased lead absorption and hypertension and cerebrovascular accident (*35*). These effects appear to be mediated both through the toxic effects of lead on the kidneys, as well as by direct action on vascular smooth muscle.

Reproductive Toxicity of Lead

A body of experimental evidence indicates that lead at high doses is toxic to reproductive function in both male and female laboratory animals (*36*). Also, clinical reports, most of them from the first half of this century, described reproductive toxicity in workers of both sexes with high-dose exposure to lead; the incidence of spontaneous abortion was reported in these studies to be increased in female lead workers, as well as in the wives of male lead workers (*37,38*).

In male workers heavily exposed to lead (mean blood lead level, 74.5 μg/dL) and also in males with moderately increased lead absorption (mean blood lead level, 52.8 μg/dL), decreased sperm counts and an increased prevalence of morphologically abnormal sperm have been reported (*39*). Corroboration of these findings is provided by recent American and Italian studies, which also observed sperm count depression at relatively high blood lead levels (> 60 μg/dL) (*40,41*). Further research will be required to delineate dose-response relationships in males for the reproductive toxicity of lead, particularly at lower levels of exposure.

Future Research Strategies

X-Ray Fluorescence Analysis

The use of XRF analysis to measure lead in bone offers major methodologic advances over present-day techniques for assessment of the chronic toxicity of lead. A major limitation on studies of lead toxicity undertaken heretofore is that they have been forced to rely largely on determination of the level of lead in blood as a biological index of exposure to lead. The half-life of lead in blood is 36 ± 5 days (*42*). The blood lead level is therefore a good indicator of recent exposure and is quite satisfactory for the assessment of effects of acute nature and relatively short duration, such as anemia or peripheral neuropathy. The blood lead level is, however, seriously deficient as an index of chronic lead exposure. Thus, it is of only limited value for assessing exposure-response relationships for such long-term consequences of exposure to lead as renal disease, hypertension, or chronic impairment of the central nervous system (*9*). For evaluation of the natural history and dose-response relationships of these effects, a measure of chronic lead exposure will be essential. Measurement of bone lead burden by XRF analysis offers a noninvasive and relatively rapid approach to the individualized assessment of chronic lead exposure.

XRF analysis may be undertaken using either K or L X-rays, and both K- and L-XRF instruments have been developed (*43,44*). The K instrument has several intrinsic methodologic advantages over the L instrument for use in industrial populations (*45*). First, the K-XRF instrument samples lead across the entire transverse section of bone, in contrast to the L instrument, which obtains 90% of its signal from only the two most superficial millimeters; if there is variation in the concentration of lead across the bone between the superficial, subperiosteal and the deeper sectors, then the L measurement will fall victim to this variation, whereas the K will not. Additionally, the K instrument is robust to small inaccuracies in measurement of the thickness of the overlying skin, whereas the L instrument is exquisitely sensitive to any error in measurement of skin thickness. A third methodologic advantage of the K instrument is that it is relatively resistant to movement of the subject during the sampling period, whereas the L instrument is sensitive to movement; given that the typical sampling time is approximately 15 min, this consideration is not trivial. In defense of the L instrument, there may be detailed modeling studies in which it will be desirable simultaneously to examine lead content in several bone compartments. In such circumstances, the combined use of the K and the L instruments might offer uniquely valuable information on the kinetics of lead in both the superficial and deeper compartments of compact bone. XRF instrumentation may find application in several types of epidemiologic studies, discussed in the following section.

Cross-Sectional Epidemiologic Studies

The K-XRF instrument appears to represent the single best tool for assessment of the chronic toxic effects of lead in cross-sectional studies of industrial populations. The K instrument may be expected to find application in cross-sectional studies to define dose-response relationships for the following toxic outcomes induced by chronic occupational exposure to lead.

Chronic Neurologic Toxicity. Further research is required to better delineate dose-response relationships between chronic exposure to lead and impairment of the peripheral and central nervous system. In particular, there is need to assess toxic effects of chronic exposure to relatively low doses of lead and to determine whether there exist thresholds for the neurotoxicity of lead, especially in the peripheral nervous system (*46*). The issue of subclinical toxicity to the central nervous system is not nearly so well-defined in adults as it is in children (*47*). Industrial populations comprise important groups in which to undertake studies of the chronic neurotoxicity of lead because of their long-term relatively intense exposure and because they are carefully defined and receive periodic monitoring of blood lead levels and air lead exposures.

Chronic Renal Toxicity. The most important research need in the study of lead nephropathy is a reliable early biologic indicator of the kidney damage induced by lead (*28*). Such a marker would permit better assessment of dose-response relationships and might

enable determination of the proportion of cases of renal failure caused by chronic exposure to lead.

Cross-sectional epidemiologic studies in industrial populations which couple sensitive biologic indicators of renal toxicity with determination of chronic lead exposure by XRF analysis of lead in bone may be expected to permit substantially better definition than heretofore of dose-response relationships for lead nephropathy. Previous attempts to define these dose-response relationships using the blood lead level as an index of exposure have largely been unsatisfactory (*9*), presumably because in the context of chronic exposure the blood lead level does not provide adequate information on the cumulative dose of lead to the kidneys.

Cardiovascular Toxicity and Hypertension. Further elucidation of the dose-response relationship between lead and hypertension and assessment of the clinical significance of lead-induced hypertension will also require the use of an integrated measure of chronic lead absorption, such as may be provided by XRF analysis of lead in bone. In future studies of lead-induced hypertension, XRF analysis, coupled with continuous monitoring of blood pressure and state-of-the-art techniques for assessment of renal physiology and catecholamine metabolism, may provide exceptionally useful data for delineating the mechanisms as well as for elucidating dose-response relationships.

Reproductive Toxicity. In addition, the K instrument may find utility in cross-sectional studies to examine the relationship between lead and reproductive dysfunction in male workers, although at least the testicular component of this effect appears mainly to be of short duration and, therefore, may be studied more effectively by use of the blood lead determination (*40*).

Toxicity and Genetic Polymorphism. Finally the K X-ray instrument may be useful in cross-sectional studies to assess toxic effects of lead exposure in relation to the genetic composition of lead workers. The hypothesis has been advanced that genetic polymorphism in the enzyme ALA-D may be associated with differential metabolism of lead and differential toxicity of lead storage (*42*). Studies in which genetic assessment of ALA-D polymorphism are combined with assessment of the body lead burden using the K-XRF instrument should be extremely useful in testing this hypothesis.

Prospective Studies

In longitudinal prospective studies of populations exposed to lead, the XRF instrument may be expected to be extremely useful. Two groups in whom prospective studies may be undertaken are new entrants to the lead industry and retirees or strikers, who are no longer exposed to lead, but who had many previous years of lead exposure. In these groups, use of the XRF technology will permit examination of either accumulation or loss of lead over time. A methodologic advance that might be particularly useful in such studies would be the simultaneous use of two K instruments plus an L instrument. One K instrument would examine the tibia and provide information on lead in dense cortical bone. The second K instrument would examine the calcaneus to provide information on lead in trabecular bone (*49*). Third, an L X-ray instrument could be used in such studies to examine the accumulation or loss of lead from the subperiosteal compartment of cortical bone.

In prospective studies of workers exposed to lead, especially if such studies were to be undertaken in closely monitored populations of industrial workers, it might be useful to compare direct estimates of bone lead burden as derived by XRF analysis with indirect estimates derived from serial measurements of blood lead levels or airborne lead exposures (*50*).

The toxic end points that might most fruitfully be evaluated in prospective studies of workers using the XRF technology include toxicity to the peripheral and central nervous system, renal toxicity, and lead-induced hypertension. In essence, it may be anticipated that these prospective studies will build upon and follow the cross-sectional epidemiologic studies discussed in the preceding section. The great methodologic advantage that will accrue from the conduct of repeated measurements of exposure and effect in the same workers over time in these prospective studies is that individual variation will largely be eliminated from the analysis as a source of background noise. In prospective studies, each subject is compared with himself or herself over time, in contrast to cross-sectional studies, in which individuals are compared with one another. Slight changes in function over time can therefore be detected with great reliability in prospective studies.

Prospective Studies Combined with Chelation Therapy

Studies of lead burden in workers undergoing therapeutic chelation offer yet another area in which the XRF technology may be extremely useful (*50*). In such studies, the use of three instruments simultaneously (two K instruments and an L instrument) to assess the movement of lead from various compartments in bone as the result of chelation would provide extremely important data. Additionally, it would be important in such studies to correlate the loss of lead from various bony compartments with possible improvements in function of various end organs, including the nervous system, the kidneys, and the reproductive organs.

Pharmacokinetic Modeling

The XRF instrumentation will be extremely important for refining existing models of the pharmacokinetics of lead (*49,50*). One of the most useful models of the body burden and pharmacokinetics of lead currently extant is that developed by Bernard and refined by Hattis (*51,52*). It posits the existence of five functional compartments. Only limited experimental validation of this model is, however, available at present. The use

of the XRF instrumentation in prospective studies, as well as in workers undergoing chelation, will be extraordinarily useful in providing validation and further refinement of this and other models.

Conclusion

In summary, worker populations will be exceptionally valuable for the assessment and further development of the XRF technology. The three particular advantages provided by worker populations for such studies are *a*) they are closely defined, *b*) they have more intense and more prolonged exposures to lead than the general population, and *c*) extensive data are available in these populations on previous air lead exposures and blood lead levels.

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